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Albumin Synthesis Rates Are Not Decreased in Hypoalbuminemic Cachectic Cancer Patients With an Ongoing Acute-Phase Protein Response

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Objective

To determine whether suppression of albumin synthesis contributes to the hypoalbuminemia observed in weight-losing cancer patients with evidence of an ongoing acute-phase protein response (APPR).

Background Data

Proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) are known to downregulate albumin synthesis and increase acute-phase protein production in isolated hepatocytes. However, whether albumin synthesis is suppressed in hypoalbuminemic cancer patients with evidence of an ongoing acute-phase response is unknown.

Methods

Albumin synthesis rates were determined in six healthy controls and in six weight-losing pancreatic cancer patients with an ongoing APPR using a flooding dose technique with [$^2H_5$]-phenylalanine. The presence of an APPR was defined as a serum C-reactive protein concentration >10 mg/L. Serum cytokines (TNF, IL-6) and soluble TNF receptors (sTNF-R 55 and 75), along with serum cortisol and insulin, were also measured in both groups.

Results

Cancer patients had reduced serum albumin (median 32 [range, 23–36] *vs.* 42 g/L [40–45]; $p < 0.01$) and increased serum C-reactive protein concentrations (72 [23–126] *vs.* <5 mg/L; $p < 0.01$) when compared with controls. TNF was not detected in either group. sTNF-R 55 levels were significantly elevated in the cancer patients (3.8 [1.9–8.1] *vs.* 1.2 pg/mL [0.9–2.2]; $p < 0.01$). Circulating IL-6, insulin, and cortisol concentrations were not significantly different between the groups. The intravascular albumin mass was lower (88 [56–93] *vs.* 133 g [105–177]; $p < 0.01$), but the intravascular albumin fractional synthetic rate was higher (13.9 [13.5–18.5] *vs.* 10.3%/d [71–11.3]; $p < 0.01$) in the cancer patients

compared with the controls. The total intravascular albumin synthetic rate was, however, similar between the two groups (12.7 [7.7–15.7] *vs.* 11.7 g/d [8.5–18.7]; p NS).

Conclusions

In weight-losing pancreatic cancer patients with evidence of an ongoing APPR, hypoalbuminemia is not caused by a decreased rate of albumin synthesis.

The factors that mediate changes in the protein metabolism of cachectic cancer patients are ill defined.[1] Recently, it has been proposed that activation of the host's own proinflammatory cytokine network may be important.[2–4] One of the key metabolic changes induced by proinflammatory cytokines is the hepatic acute-phase protein response (APPR), and as such an ongoing APPR may reflect proinflammatory cytokine activity *in vivo*. It is therefore of interest that C-reactive protein (a prototypical positive acute-phase reactant) is often increased in recurrent or advanced malignancy.[5] Moreover, increased circulating C-reactive protein is associated with increased energy expenditure[6] and a shortened duration of survival in some types of cancer patients.[7] The hypoalbuminemia observed in cancer patients may also reflect an ongoing APPR. Albumin is the principal negative acute-phase reactant in humans, and a reduction in the serum concentration of this protein is an established marker of poor prognosis in various diseases, including malignancy.[8] However, in a situation where patients are losing weight, such hypoalbuminemia may be as much a result of protein–calorie undernutrition as of a negative acute-phase response.

When isolated hepatocytes are incubated in the presence of proinflammatory cytokines, the synthesis of positive acute-phase proteins (*e.g.*, C-reactive protein) is increased, whereas that of the negative acute-phase proteins (*e.g.*, albumin) is reduced.[9,10] However, whether these cytokines exert a similar bifunctional role in the acute-phase response of weight-losing cancer patients is unknown. Similarly, the endocrine hormones insulin and cortisol are known to modulate cytokine-induced hepatocyte export protein production,[11] but their role in the altered hepatic metabolism of cancer patients is not established. We have previously demonstrated elevated plasma concentrations of interleukin 6 (IL-6) in a group of weight-losing colon cancer patients who had increased circulating levels of C-reactive protein and marked hypoalbuminemia.[12] The aim of the present study was to determine in a group of pancreatic cancer patients with a positive acute-phase protein reaction whether hypoalbuminemia is caused by a decrease in albumin synthesis and how this relates to circulating cytokine and endocrine hormone profiles.

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MATERIALS AND METHODS

Subjects

Six patients with histologically proven pancreatic cancer who were losing weight, had no clinical evidence of ascites or peripheral edema, and had an ongoing APPR (C-reactive protein >10 mg/L) participated in the study. Six patients admitted for minor elective surgery (*e.g.*, inguinal hernia repair) served as weight-stable controls. The latter had no evidence of an acute-phase response. None of the cancer patients had received chemotherapy or radiation therapy, and neither group had undergone surgery within the preceding 2 months. All persons were of performance status 2 or better (World Health Organization performance score) and were judged clinically to be free of other metabolic or endocrine disorders. None were pyrexial, had clinical or radiologic evidence of infection, were receiving steroids, or were severely anemic.

Study Protocol

After an overnight fast, venous catheters were inserted into each antecubital fossa. One catheter was used to administer an infusion over 10 minutes of [$^2H_5$]-labeled phenylalanine (3.5 g 10 mole % phenyl-[$^2H_5$]-L-phenylalanine, 2% saline; Tracer Technologies, Sommerville, MA). This was coadministered with a plasma volume tracer (15 mg Evan's blue in 3 mL saline; Fluka Chemicals, Derbyshire, United Kingdom). Both solutions had been passed through a micropore filter (0.22-μm pore, single-use filter; Millipore, Molsheim, France) under aseptic conditions before being dispensed in ampules by the pharmacy department at the Western General Hospital, Edinburgh, United Kingdom. The catheter in the opposite arm was used to obtain 10-mL blood samples before and 10, 20, 40, 60, 80, and 120 minutes after the infusion of [$^2H_5$]-labeled phenylalanine. Blood was aliquoted into glass tubes for serum and lithium heparin tubes for plasma. Blood samples were centrifuged at 2000 r.p.m. and stored at −70 C. The plasma samples collected

before the flooding dose were analyzed for [$^2H_5$]-phenylalanine enrichment in plasma albumin and in the plasma-free phenylalanine pool. Plasma volume was estimated from the dilution of Evan's blue using the plasma samples taken at 0, 10, and 20 minutes.[13] Baseline serum samples (taken before the labeled phenylalanine infusion) were assayed for albumin, C-reactive protein, IL-6, tumor necrosis factor [TNF], and soluble TNF receptors (sTNF-R55 and 75). Baseline plasma samples were assayed for insulin and cortisol.

The study was approved by the ethics committee of the Lothian Health Board. All patients were informed of the purposes and procedures of the study, and all gave written informed consent.

Cytokine and Soluble Cytokine Receptor Assays

TNF was measured using an indirect enzyme-linked immunosorbent assay (ELISA) as described by the manufacturers (Boehringer-Mannheim, Lewes, United Kingdom). Samples were diluted 1:5. The limit of detection of the assay was 15 pg/mL. IL-6 was measured by sandwich ELISA, as described previously.[14] The lower limit of detection of the assay was 50 pg/mL. Type I and type II sTNF-R (sTNF-R55 and 75, respectively) were detected by sandwich ELISA using antibodies kindly donated by Dr. W. Buurmann (Academisch Ziekenhuis, Maastricht, The Netherlands), as described previously.[15] The lower limit of detection of the assay was 0.39 ng/mL for both receptors. The interassay coefficient of variation for all cytokine and soluble receptor assays was <10%.

Serum Proteins and Endocrine Hormone Assays

Albumin concentrations were measured using the bromocresol green method[16] on a Technicon RA-1000 automated analyzer (Technicon Instruments, Tarrytown, NY). C-reactive protein was measured by fluorescent polarization immunoassay using an Abbott TDX analyzer and Abbott reagents (Abbott Laboratories, Maidenhead, United Kingdom). The limit of detection of the assay was 5 mg/L. Insulin concentrations were measured with radioimmunoassay (Institute of Biochemistry, Royal Infirmary, Glasgow, United Kingdom) using Sepharose covalently linked to a second antibody as the separation system. The fasting reference range was <13 mU/L. The between-batch coefficient of variation was 10.5% at a concentration of 30 mU/L. Cortisol concentrations were measured by radioimmunoassay (Institute of Biochemistry, Royal Infirmary, Glasgow, United Kingdom) using antisera obtained from the Scottish Antibody Production Unit (Carluke, United Kingdom). Separation of the assay was performed using a solid phase technique. The limit of detection was 40 nmol/L, and the between-batch coefficient of variation was <10% across the working range of the assay.

Sample Preparation and Isotope Analysis

The study protocol involved the measurement of [$^2H_5$]-phenylalanine enrichment in the plasma-free phenylalanine pool and in plasma albumin. For free phenylalanine analysis, plasma samples were diluted with distilled deionized water and cycloleucine (250 nmol/mL plasma) was added as an internal standard. Samples were then deproteinized by ultrafiltration and acidified, and the amino acids were purified by cation exchange. [$^2H_5$]-phenylalanine enrichment was measured by gas chromatographic mass spectrometry as its tertbutyldimethylsilyl derivative.[17]

Albumin was extracted from 1 mL of plasma by differential solubility in absolute ethanol from trichloroacetic acid (10% w/w)-precipitated protein.[18] To remove traces of free phenylalanine, the ethanolic albumin solution was washed three times with 5 mL distilled deionized water using an ultrafiltration device (molecular weight [MW] cutoff <25,000; Amicon, Gloucestershire, United Kingdom), and centrifuged at 10,000*g* for 25 minutes. The purity and identity of the extracted albumin was confirmed using sodium dodecyl sulfate–glycerol polyacrylamide gel electrophoresis[19] calibrated with a series of molecular markers. Purified albumin was then hydrolyzed[20] and [$^2H_5$]-phenylalanine enrichment measured.[17]

Calculations

Fractional synthesis rates for albumin were calculated by dividing the rate of change of [$^2H_5$]-phenylalanine enrichment of albumin by the area under the curve of precursor enrichment *versus* time, as described by Ballmer et al.[21] Similarly, the secretion times for these proteins were calculated as described previously.[21]

Statistics

Data are presented as median and range. Where appropriate, data were tested for statistical significance using the Mann-Whitney U test, and comparison of paired data was carried out using the Wilcoxon signed rank test (Minitab, Pasadena, CA). Differences were considered significant when the chance of their occurrence by sampling error was <1 in 20 ($p < 0.05$).

Table 1. CLINICAL CHARACTERISTICS OF CANCER PATIENTS AND WEIGHT STABLE CONTROLS

	Controls	Cancer Patients	p
Sex (M:F)	4:2	3:3	NS
Age (yr)	64 (48–69)	65 (48–70)	NS
Height (cm)	168 (159–178)	167 (152–168)	NS
Weight (kg)	66 (57–70)	56 (52–59)	<0.05
Weight loss (%)*	0	18 (14–25)	<0.01

NS = not significant.
Values are median (range).
* As a percentage of pre-illness stable weight.

RESULTS

The clinical characteristics of the control group and cancer patients are shown in Table 1. The groups were well matched for age, sex, and height. The cancer patients had lost approximately 18% of their preillness stable weight and were significantly lighter than the weight-stable controls ($p < 0.05$).

The median circulating albumin concentration, plasma volume, and albumin kinetics are shown in Table 2. The median albumin concentration of the cancer patients was below the reference range (36–47 g/L) and was significantly lower than that of the controls (32 *vs.* 42 g/L, $p < 0.01$). There was no significant difference in plasma volume or albumin secretion time between the two groups. Albumin intravascular mass (88 *vs.* 133 g, $p < 0.01$) was decreased but its fractional synthetic rate was increased (13.9 *vs.* 10.3%/d, $p < 0.01$) in the cancer group when compared with the controls. The total albumin synthesis rate was not significantly different between the two groups (12.7 *vs.* 11.7 g/d, p NS).

The circulating acute-phase protein and mediator profiles of the controls and cancer patients are shown in Table 3. The median circulating C-reactive protein concentration was <5 mg/L (below the limit of detection) in the control subjects compared with a median value of 72 mg/L in the cancer patients ($p < 0.01$).

The circulating concentrations of insulin and cortisol were not significantly different between the two groups, but the median cortisol:insulin ratio was significantly increased in the cancer patients compared with the control group (see Table 3). TNF was not detected in any of the cancer patients or controls. In contrast, sTNF-R55 and 75 were detected in the plasma of all the subjects studied, and the concentrations of both receptors were significantly higher in the cancer patients than in the controls ($p < 0.01$). IL-6 was detected in three of the six cancer patients and in none of the controls, but this difference was not statistically significant ($p = 0.06$).

DISCUSSION

In our study, cancer patients with hypoalbuminemia and an ongoing APPR had an increased albumin fractional synthetic rate when compared with healthy controls (see Table 2). However, the intravascular albumin mass of the cancer patients was reduced, and thus their total albumin synthetic rate was similar when compared with controls (see Table 2). Therefore, in weight-losing pancreatic cancer patients, hypoalbuminemia is not caused primarily by a reduction in albumin synthesis, and other factors need to be considered.

Previously, an increased rate of albumin distribution from the intravascular to the extravascular fluid compartments had been proposed as part of the mechanism whereby hypoalbuminemia occurs in both cancer and sepsis.[22] However, recent work suggests that the changes in transcapillary escape rates observed in at least some advanced cancer patients with hypoalbuminemia are relatively small and overall do not correlate with circulating

Table 2. PLASMA VOLUME AND ALBUMIN SYNTHETIC RATE IN NORMAL SUBJECTS AND PATIENTS WITH CANCER

	Control Subjects (n = 6)	Cancer Patients (n = 6)	p
Plasma albumin (g/L)	42 (40–45)	32 (23–36)	<0.01
Plasma volume (mL)	3122 (2483–4326)	2623 (2449–2881)	NS
Intravascular albumin mass (g)	133 (105–177)	88 (56–93)	<0.01
Albumin secretion time (min)	28 (22–32)	25 (19–28)	NS
Albumin fractional synthetic rate (%/day)	10.3 (7.1–11.3)	13.9 (13.5–18.5)	<0.01
Albumin total synthetic rate (g/day)	11.7 (8.5–18.7)	12.7 (7.7–15.7)	NS

NS = not significant.
Values are median (range).

Table 3. CIRCULATING PROTEINS/MEDIATORS IN NORMAL SUBJECTS AND PATIENTS WITH CANCER

	Control Subjects (n = 6)	Cancer Patients (n = 6)	p
C-reactive protein (mg/L)	<5	72 (23–126)	<0.01
Insulin (mU/L)	3.8 (2.3–8.4)	2.2 (0.6–5.5)	NS
Cortisol (nmol/L)	415 (272–666)	577 (407–916)	NS
Cortisol:insulin ratio	101 (58–162)	241 (167–800)	<0.01
Interleukin-6 (pg/mL)	<50	74 (<50–181)	NS
TNF (pg/mL)	<15	<15	NS
sTNFR55 (pg/mL)	1.2 (0.9–2.2)	3.8 (1.9–8.1)	<0.01
sTNFR75 (pg/mL)	2.6 (1.5–3.0)	7.5 (3.9–20.1)	<0.01

NS = not significant.
Values are median (range).

albumin concentrations.[14] It has also been reported that cachectic cancer patients have a relative expansion of their extracellular water space.[23] But for this to act as an extended reservoir for albumin derived from the intravascular compartment, there would have to be an absolute expansion of the space. Extracellular water space was not measured in the present study. However, the cancer patients did not have gross evidence of ascites or peripheral edema, and therefore it cannot be assumed that their extracellular space was increased. Lastly, an increase in albumin degradation without a corresponding increase in synthesis could account for the observed hypoalbuminemia. Increased albumin degradation rates have been documented in patients with chronic inflammation.[24] However, using ^{131}I-labeled albumin, Steinfeld[25] reported reduced albumin degradation in a heterogeneous group of patients with advanced cancer. There are, however, many difficulties with the measurement of albumin degradation rates *in vivo*.

In our study, neither TNF or IL-6 was consistently isolated from the serum of the cancer patients (see Table 3). However, we have previously documented in patients with pancreatic cancer and an ongoing APPR upregulated proinflammatory cytokine release by isolated peripheral blood mononuclear cells,[6] and this may reflect more accurately tissue cytokine production rates. In the present study, both of the soluble receptors for TNF (sTNF-R 55 and 75) were detected at higher concentrations in the plasma of the cancer patients compared with the controls (see Table 3). Soluble TNF receptors are shed during an acute-phase response, and again this may indicate activity of TNF within the tissues.[26]

Previously, Brenner et al[27] showed profound hypoalbuminemia and reduced hepatic albumin mRNA levels in mice transplanted with Chinese hamster ovary cells transfected with the functional gene for human TNF-alpha. These changes occurred before the animals became cachectic, suggesting that the effects on albumin were not secondary to undernutrition. They could not, however, exclude generation of other cytokines (*e.g.*, IL-6) *in vivo* as a mechanism for the TNF response. Such data suggest that in an acute-phase response caused primarily by the action of IL-6 or TNF on the liver, hypoalbuminemia would result from a suppression of the albumin synthetic rate. In the present study, despite an increase in C-reactive protein production, total albumin synthesis rates were not suppressed in the cancer patients. This suggests a more complex regulation of the acute-phase response than by IL-6 or TNF alone. However, one of the main stimuli for hepatocyte albumin production is the ambient serum colloid osmotic pressure,[28] and thus in hypoalbuminemia one might expect a compensatory rise in albumin synthesis. Thus, the apparently "normal" rate for albumin total synthesis observed in the present study may represent cytokine-induced suppression of a compensatory response.

In our study, plasma insulin and cortisol concentrations were not significantly different between cancer patients and controls. However, when hormone concentrations were expressed as a ratio (cortisol:insulin), this was significantly higher in the cancer patients than in the controls. Both insulin and cortisol are known to influence the pattern of acute-phase proteins synthesized by isolated human hepatocytes,[9,11] and Dahn et al.[29] have shown that TNF-induced suppression of albumin synthesis in isolated hepatocytes is abrogated by insulin or nutrient (glucose) deprivation. To determine the precise role neuroendocrine hormones play in the regulation of the APPR *in vivo* will clearly require much further study.

In conclusion, it has been suggested that in the semistarving host, the mismatch between the amino acid composition of acute-phase proteins and those of the main labile amino acid reserve in the body (*i.e.*, skeletal muscle) may account for accelerated wasting of lean tissue

during an APPR.[30] If such a hypothesis is correct, then further detailed understanding of the factors that regulate both positive and negative acute-phase proteins *in vivo* may allow better targeting of therapy to arrest the nutritional and metabolic decline of the cancer patient. The present study suggests that it may not be possible to predict targets for such therapy from *in vitro* studies alone.

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